HPV Grease Thickeners Test Plan
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HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

TEST PLAN

Fatty Acids, Lithium & Calcium Salts
used as
Grease Thickeners

Submitted to the US EPA

by

The Petroleum HPV Testing Group

www.petroleumhpv.org

Consortium Registration

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TEST PLAN

GREASE THICKENERS CATEGORY

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PLAIN LANGUAGE SUMMARY

The lithium and calcium salts of fatty acids in this category are used by the lubricants industry to thicken greases. For this use they are not synthesized as the "pure" compounds but are made only in the presence of oil. One or more fatty acids is dissolved in mineral oil and then a caustic such as calcium hydroxide or lithium hydroxide is added. The caustic and fatty acid molecules react to form the insoluble metal salt of the fatty acid. The resulting compounds gel the mineral oil into a functional grease. Greases typically contain from approximately 1- 14 % thickener by mass.

The calcium and lithium salts of fatty acids used as grease thickeners in this category are considered very low in toxicity based on extensive use in industry without reports of significant adverse effects for many decades. The fatty acids from which the salts are made are either edible or similar in structure to edible fatty acids. The salts formed in the presence of mineral or synthetic oils are not readily bioavailable due to size and limited solubility in the grease matrix.

Results from testing lithium fatty acid salts, fatty acid salts compositionally similar to salts in this category (eg. magnesium stearate) and greases containing thickeners from this category, demonstrate that these materials are not acutely toxic by the oral or dermal route, are not irritating to the eyes or skin and do not induce skin sensitization. Repeat dose studies in rats by the oral route (Mg stearate – 3 months in diet; castor oil – 13 wks in diet; lithium complex grease –90 days by oral gavage), or with dermal treatment (lithium complex grease – 28 or 90 days) did not show any significant adverse effects. Treatment with a lithium grease dermally for 2 years did not cause skin cancer in C3H mice. Mutations were not induced in bacterial assays by fatty acids used to make salts in this category. Soluble lithium salts were not mutagenic *in vitro*, and slight chromosomal effects occurred only from a very high dose of lithium citrate administered intraperitoneally. Considering, along with these data, the low solubility of salts of fatty acids in the grease thickeners category, the compounds are not unlikely to be mutagenic. No developmental or reproductive toxicity assays are available for lithium salts of fatty acids in this category. Magnesium stearate (structurally similar to calcium stearate) did not induce developmental effects in orally treated pregnant rabbits. Two calcium salts in this category are not considered candidates for SIDS testing under the HPV Challenge Program.

Substances in the grease thickeners category can be considered environmentally innocuous due to their origin from alkali metals and edible fats and oils (or similar fatty acids) and their low water solubility. The hydrocarbon components of the greases have little or no tendency to

partition into air, are not susceptible to hydrolysis or direct photolysis under environmental conditions, and will partition primarily to soil and sediment. Fatty acids are known to be used by microorganisms as a source of energy, and the calcium and lithium salts of fatty acids are biodegradable. Technical discussions and computer modeling will be used to address physicochemical and environmental fate endpoints.

A technical discussion will be prepared for the robust summary that describes the potential for substances in this category to affect aquatic organisms. Due to the process of creating the fatty acid salts “in situ” within the oil matrix, exposure to aquatic organisms by these substances is unlikely. Therefore, aquatic toxicity testing of these products would not further the understanding of their aquatic hazard, and therefore such testing is not warranted. Aquatic toxicity data on the dissociation products of these grease thickeners, i.e., lithium, calcium, and the associated fatty acids, will be included in the technical discussion along with relevant physicochemical information affecting their distribution in aquatic environments.

The test plan proposes the performance of a dermal reproductive/ developmental toxicity screening test (OECD 421) in rats using a greases thickened with approximately 12% lithium 12-hydroxystearate and no additives present. Results of this study combined with currently available data on calcium and lithium salts and compositionally similar salts of fatty acids, as well as test results from greases thickened with these salts are adequate to complete the hazard profile for materials in this category.

Description of the Grease Thickeners Category

Fatty acids, calcium & lithium salts are used by the lubricant industry to thicken greases. Most lubricants are mixtures but greases are one of the few types of lubricants that involve an actual chemical reaction during their manufacture. Although a few greases are thickened with viscous petroleum products similar to asphalt, most are made by the formation of a “soap” within a mineral oil matrix. One or more fatty acids is dissolved in mineral oil and then a caustic such as calcium hydroxide or lithium hydroxide is added. The caustic and fatty acid molecules react to form the insoluble metal salt of the fatty acid. The resulting compounds gel the mineral oil into a functional grease. Greases containing these compounds typically contain from 1-14% thickener on a mass basis.

If fatty acids or triglycerides are reacted with caustic outside of a mineral oil matrix, the resulting compounds are called soaps, hence the use of this term relative to grease thickeners of this type. Water or methanol is usually formed during the reaction depending on whether the fatty acid or its methyl ester, respectively, was used as a starting reactant. Additional performance additives such as extreme pressure agents and antioxidants may be added to a grease before or after thickening. Some greases are thickened with the lithium salt of two different fatty acids and these may be called “lithium complex” greases. Greases thickened with aluminum, calcium or lithium soaps have been widely and safely used for several decades.

The fatty acids used to make greases are derived from edible animal fats or vegetable oils. The fatty acids used as starting materials in this category are mostly monocarboxylic acids and include stearic acid (C_{18}), 12-hydroxystearic acid, docosanoic acid (C_{22}), hydrogenated castor oil (comprised of ricinoleic and similar acids, C_{18}), and methyl esters of oxidized hydrocarbon waxes ($C_{\geqslant 18}$). One lithium salt of a dicarboxylic acid (azelaic, C_9) is included in the category as it is commonly used in lithium complex greases. Azelaic acid (nonanedicarboxylic acid) is manufactured from ricinoleic acid (castor oil).

The metal salts in this HPV category are lithium or calcium. There are 11 CAS numbers in the HPV Grease Thickeners category. Some of the compounds were included in the original list sponsored by the API (1999) based on the EPA 1990 IUR, and other non-HPV materials have been added due to their structural similarity. The 11 category members are listed in Table 1.

Table 1: HPV Grease Thickeners Category

CAS #	Name	Synonym
3159-62-4	Octadecanoic acid, 12-hydroxy-, calcium salt (2:1)	Calcium 12-hydroxystearate
38900-29-7	Nonanedioic acid, dilithium salt	Dilithium azelate
4485-12-5	Octadecanoic acid, lithium salt	Lithium stearate
4499-91-6	Docosanoic acid, lithium salt	Lithium docosanoate
53422-16-5	Octadecanoic acid, 12-hydroxy-, methyl ester, lithium salt	Lithium 12-hydroxystearate (same as 7620-77-1)
64754-95-6	Castor oil, hydrogenated, lithium salt	
68783-36-8	Fatty acids, C_{16-22}, lithium salts	
7620-77-1	Octadecanoic acid, 12-hydroxy-, monolithium salt	Lithium 12-hydroxystearate (same as 53422-16-5)
1592-23-0	Stearic acid, calcium salt	Calcium stearate
64755-01-7	Fatty acids, tallow, calcium salts	
68603-11-2	Hydrocarbon waxes, petroleum, oxidized, Me esters, calcium salts	

Two compounds in the category have different CAS numbers and slightly different names but are chemically the same. Lithium 12-hydroxystearate is formed from both the methyl ester of 12-hydroxy octadecanoic acid and from the acid itself. If the methyl ester is used, then methyl alcohol is formed as a byproduct instead of water.

Two other compounds in this category [Stearic acid, calcium salt (CAS 1592-23-0) and Fatty acids, tallow, calcium salts (CAS 64755-01-7)] are considered adequately characterized relative to the Screening Information Data Set. These two compounds are designated “1” and the EPA has concluded that the “Chemical is not considered a candidate for testing under the HPV Challenge Program, based on preliminary EPA review indicating that testing using the SIDS base set would not further our understanding of this chemical’s properties” (EPA HPV Challenge Program Chemical List).

Typical Properties

Table 2 summarizes the typical physical and chemical properties that characterize the calcium and lithium salts in this category and some closely-related compounds.

Table 2: Physicochemical properties of fatty acid salts used as grease thickeners and related compounds

Compound	Carbon number	Molecular wt.	Melting point (°C)	Water solubility
Category members:				
Calcium 12-hydroxystearate	18	640		
Calcium stearate	18	608	179	0.004g/100cc @15^{0}C
Fatty acids, tallow, calcium salts	14-18	> 490		
Hydrocarbon waxes, petroleum, oxidized, Me esters, calcium salts	> 18	> 600		
Lithium stearate	18	291	220-221 (CIR)	"insoluble" (CIR)
Lithium 12-hydroxystearate	18	307		
Castor oil, hydrogenated, lithium salt	> 16	> 260		
Fatty acids, C_{16-22}, lithium salts	16-22	~263-347		
Lithium docosanoate	22	347		
Dilithium azelate	9	202		
Related compounds:				
Sodium stearate	18	308		"slowly soluble"
Magnesium stearate	18	591	88 ?; 132	0.003g/100cc @15^{0}C
Zinc stearate	18	632	130	"insoluble"
Sodium oleate	18	305	232-235	10g/100cc@ 12^{0}C
Potassium oleate	18	322	235-240	25g/100cc cold water
Sodium palmitate	16	278	270	"insoluble"

CATEGORY JUSTIFICATION AND TEST MATERIAL DESCRIPTION

All of the compounds in this category are the lithium or calcium salt of similar fatty acids. All of the fatty acids are similar in size (14 carbons long or longer) with the exception of nonanedioic acid (azelaic), which contains 9 carbons. Stearic acid is found in food, and similar to castor oil, is used in cosmetics and pharmaceuticals. These and the other fatty acids are similar in chemical characteristics. Several of these fatty acids are HPV chemicals sponsored by other chemical manufacturers. All of these salts of fatty acids synthesized "in situ" in a mineral oil matrix and their biological activity is low because of high molecular weight and insolubility. Therefore testing from one compound can be extrapolated to likely effects of other category members.

The material selected for this test plan is a lithium salt thickened grease synthesized from USP white mineral oil and approximately 12% lithium 12-hydroxystearate. Since for lubricant purposes, fatty acid salts are only formulated in the presence of petroleum oil, this lithium grease thickener will be tested in a petroleum oil matrix.

EVALUATION OF EXISTING HEALTH EFFECTS DATA AND PROPOSED TESTING

Introduction

The calcium and lithium salts of fatty acids used as grease thickeners in this category are considered very low in toxicity based on their extensive use without reports of significant toxicity for many decades. A very large population of workers has had frequent dermal exposure while using greases for the lubrication of bearings and other moving parts in virtually every segment of transportation and industry.

The compounds in this category are made from fatty acids that are either edible or similar in structure to edible fatty acids. These fatty acids in their free state are readily absorbed from the gastrointestinal tract and readily metabolized. The calcium and lithium salts that are formed in the presence of mineral or synthetic oils, however, are not readily bioavailable and their function is to maintain the oils in a gel-like state in contact with the surfaces being lubricated. High resistance to water wash-out is a desirable trait of most greases.

Calcium is common in all living systems and is essential to life. Lithium ion is used pharmacologically to treat bipolar disorder and is toxic at higher plasma concentrations. Lithium has significant bioavailability only when administered as a partially soluble salt such as lithium carbonate. Both the calcium and lithium salts of the fatty acids in this category, especially when present in an oil matrix, have extremely low bioavailability.

Toxicological data on several stearic acid compounds including the aluminum, calcium, and lithium salts, were reviewed by the Cosmetic Ingredient Review (CIR) Panel (1982).

Toxicological studies of calcium and lithium salts of fatty acids in their pure form and studies with greases thickened with these salts are both considered relevant to an assessment of their hazards.

Study Review and Evaluation

Results of studies on materials in this category and materials similar to those in this category are summarized in this section. Detailed study information is available in the Robust Summaries organized in the IUCLID data set format employed by the European Union (Appendix 1). The currently available data submitted to the HPV program and any additional testing will be developed with the goal of facilitating international harmonization of hazard and risk characterization worldwide.

Acute Toxicity

Calcium salts of fatty acids:

There are no acute toxicity data for the calcium salts *per se*. However, data may be extrapolated from available information on magnesium salts such as Mg stearate (oral LD50 > 10 g/kg; CIR, 1982). Ca stearate is cleared as a direct food additive and is considered GRAS (Generally Recognized as Safe).

Mg stearate was not irritating when tested on the skin or in the eyes of rabbits (CIR, 1982).

Lithium salts of fatty acids:

The oral LD50 of Li stearate in the rat is > 5 g/kg (CIR, 1982). A lithium complex grease containing 13.1% lithium 12-hydroxystearate and 2.6% dilithium azelate had an oral LD50 in the rat > 5 g/kg (Pharmakon, 1994a). This same grease had a dermal LD50 in the rabbit > 3 g/kg (Pharmakon, 1994b) and did not induce acute skin or eye irritation potential (Pharmakon, 1994 c,d).

Another lithium complex grease containing 8.8% lithium hydroxystearate and 1.8% dilithium azelate was tested for skin sensitization potential using a Buehler assay. This grease, which also contained several performance additives, was negative for sensitization (Pharmakon, 1997).

Summary: The data available demonstrate that the substances in this group are not acutely toxic by either the oral or dermal routes. They are non-irritating to the skin and eye and are not sensitizing to the skin. Both calcium and lithium stearates have been safely used in cosmetics and lithium stearate has been used in baby powders to aid in water repellency and oil absorbency (CIR, 1982). **There are sufficient data to characterize this group of substances for acute toxicity. No additional testing is proposed.**

Repeated Dose Toxicity

Calcium salts of fatty acids:

No 28-day or longer studies are available on the calcium compounds in this category. However, data may be extrapolated from a study with magnesium stearate. Rats were fed Mg stearate up to 20% in the diet for 3 months (Sondergaard et al., 1980). There were no significant histopathologic changes. The NOEL was 5% (~ 2500 mg/kg/day).

Lithium salts of fatty acids:

A lithium complex grease containing 8.8 % lithium 12-hydroxystearate and 1.8% dilithium azelate was tested in a 90-day oral study (Huntingdon, 1977) and in 28-day and 90-day dermal studies (Huntingdon, 1997a,b) in the rat. This grease also contained performance additives at a total concentration of about 7 percent. There were no significant adverse effects after 90 days of oral dosing with the grease at 1000 mg/kg/day or after 2100 mg/kg/day dermally. Therefore, the NOEL for lithium 12-hydroxystearate was 88 mg/kg/day orally and 185 mg/kg/day dermally. The NOEL for dilithium azelate was 18 mg/kg/day orally and 38 mg/kg/day dermallly.

Another study that is relevant to both the calcium and lithium salts in this category is a 13-week dietary study in rats and mice with castor oil conducted by the National Toxicology Program (1992). The predominant fatty acid in castor oil is ricinoleic acid (12-hydroxy-*cis*-9-octadecenoic acid) while 12-hydroxystearic acid is 12-hydroxyoctadecanoic acid. Diets containing up to 10% castor oil had no adverse effects.

Grease containing 7.5 percent lithium 12-hydroxystearate was tested in a chronic skin-painting study with 50 male and 50 female C3H/HeJ mice (Barkley and Stemmer, 1984). This grease also contained performance additives at a total concentration of about 12 percent. The total tumor incidence was 3/100. Since a tumor incidence of at least 4 percent is considered positive, the results of this assay were negative for carcinogenicity.

Summary: Repeated dose studies including a chronic skin-painting study have been conducted with greases containing lithium 12-hydroxystearate and/or dilithium azelate. Studies have been conducted with magnesium stearate, which is closely related to calcium stearate. A study has been conducted with castor oil (mostly ricinoleic acid) which is closely related to the larger fatty acids used to make the salts in this category. Results of reported studies on similar compounds are used for read-across to the grease thickeners in this category. **No additional testing is proposed.**

Genotoxicity (*in vitro* and *in vivo*)

No studies have been published/reported on the genotoxicity of either calcium or lithium salts in this category. However, castor oil and magnesium stearate have been tested in the Ames test and were negative for mutagenicity (NTP, 1992; Litton Bionetics, 1976, respectively). Thus, there is no suggestion that the fatty acids used to make the salts in this category are genotoxic. The genotoxicity of lithium compounds has been tested and reviewed (Léonard et al., 1995). The overall evidence from several *in vitro* and *in vivo* studies with soluble lithium salts indicated no mutagenic activity and a possible effect on chromosomes only after a very high intraperitoneal dose of lithium citrate (2 g/kg).

Summary: Based on the low solubility of the lithium salts of fatty acids in this category and the existing data on lithium, **no additional testing is proposed.**

Reproductive Toxicity

No studies have been reported on the reproductive toxicity of calcium salts of fatty acids in this category. The toxicity of a vehicle containing 5.5 percent magnesium stearate was tested orally in pregnant rabbits at a dose of 2.5 mg/kg (Gottschewski, 1967). There were no teratogenic effects.

No studies have been reported on the reproductive toxicity of lithium salts of fatty acids in this category.

Rats and mice were fed diets containing up to 10 percent castor oil for 13 weeks. No significant effects were observed in screening for male reproductive endpoints or length of female estrous cycles (NTP, 1992).

Summary: Since the fatty acids used to make the salts in this category are edible themselves or closely related to edible fats and oils, hazard characterization is focused on the metal ions, calcium and lithium. Relative to two of the calcium salts in the category, it has been concluded that the “Chemical is not considered a candidate for testing under the HPV Challenge Program, based on preliminary EPA review indicating that testing using the SIDS base set would not further our understanding of this chemical’s properties” (EPA HPV Challenge Program Chemical List). **Therefore, no testing of other calcium salts is proposed.**

The use of partially soluble lithium salts in the treatment of psychological conditions has been associated with developmental toxicity. A causative relationship has not been established between the ingestion of lithium pharmaceuticals and birth defects. This issue was reviewed by Léonard, et al. (1995). The lithium salts in this category are not considered soluble. However, given the lack of data for the lithium salts of fatty acids in this category, **the HPV Test Group proposes to conduct a dermal reproductive/developmental study on a grease with a lithium fatty acid salt as thickener.**

EVALUATION OF PHYSICOCHEMICAL AND ENVIRONMENTAL FATE DATA AND PROPOSED TESTING

Although some data for products in this category exist, not all of these endpoints are defined and a consensus database for chemicals that represent products in this category does not exist. Therefore, calculated and measured representative data will be identified and a technical discussion provided, where appropriate. The EPIWIN© computer model, as discussed in the US EPA document entitled "The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program", will be used to calculate physical-chemical properties of substances in this category (U.S. EPA, 2000).

A fundamental characteristic of the fatty acid salts in this category is that in their pure form, they dissociate into the free metal and fatty acid anion. The pH of an aqueous solution of these substances where 50% of the total substance is in the molecular and dissociated forms is termed its pKa. A lowering of the pH relative to its pKa shifts the equilibrium to the dissociated forms, while raising the pH relative to its pKa shifts the equilibrium to the molecular form. Therefore, knowing the pKa of a substances provides information on the predominant form of the molecule at a given pH. While pKa values for the specific substances in this category were not available, pKa values of analogous metal salts of fatty acids were found to be circumneutral, meaning that the salt and free acid anion would both exist at typical environmental pHs. When measured data cannot be found for substances in this category, data for similar compounds and modeled data will be used to describe the physicochemical and environmental fate endpoints.

Physicochemical Data

Grease thickeners included in this category are all calcium or lithium salts of fatty acids. The hydrocarbon chain lengths vary from nine carbon atoms (nonanedioic acid, dilithium salt; CAS No. 38900-29-7) to greater than 18 (hydrocarbon waxes, oxidized, methyl esters, calcium salts, CAS NO. 68603-11-2, and fatty acids, C_{16-22}, lithium salts, CAS No. 68783-36-8). For the HPV endpoints, melting point, boiling point, vapor pressure, partition coefficient and water solubility, a technical discussion will be prepared in the robust summary that describes these endpoints. Measured data on specific structures in this category will be provided, when available, and supplemented with physicochemical data of chemically similar analogs as well as estimates made using the EPIWIN© model (EPA 2000).

Summary: A technical discussion for melting point, boiling point, vapor pressure, partition coefficient and water solubility will be developed for the robust summary that includes measured data on specific category structures, chemical analogs, and estimated properties made by EPIWIN© (EPA 2000).

Environmental Fate Data

Environmental fate endpoints include biodegradation, photodegradation, hydrolysis, and distribution in the environment (fugacity). The physicochemical properties and molecular structure of a chemical will influence the degradation processes it may be subjected to in the environment, as well as the way in which it partitions among environmental compartments (e.g., air, water, soil, sediment).

Because the compounds in this category are made from fatty acids that are either edible or similar in structure to edible fatty acids, the hydrocarbon moieties of the calcium or lithium salts are expected to be inherently biodegradable in the environment. Free calcium or lithium resulting from the dissociation of the salt would be expected to engage in chemical reactions with other naturally occurring anions in a manner predictable within the thermodynamic boundaries specific to these cations. No biodegradation data were available for the materials in this category. However, these substances are similar to other fatty acids used in the food and cosmetic industry. Therefore, a technical discussion on the potential for these substances to undergo biodegradation will be developed in the robust summary. Data from chemically similar analogs of fatty acids and/or degradation estimates will be presented in the technical discussion.

For the photodegradation endpoint, estimates of the atmospheric oxidation potential will be calculated. Hydrolysis is not a relevant endpoint for substances in this category because these materials do not contain chemical linkages subject to hydrolysis.

Equilibrium models are used to calculate chemical fugacity that can provide information on where a chemical is likely to partition in the environment. These data are useful in identifying environmental compartments that could potentially receive a released chemical. Fugacity data can only be calculated. In its guidance document for HPV data development, the U.S. EPA states that it accepts Level I fugacity data as an estimate of chemical distribution values. The input data required to run a Level I model include basic physicochemical parameters;

distribution is calculated as percent of chemical partitioned to different environmental compartments within a standardized regional environment. Level I data are basic partitioning data that allow for comparisons between chemicals and indicate the compartment(s) to which a chemical is likely to partition in the environment. Estimates of the percent distribution for various environmental media (i.e., soil, water, air, sediment, biota) will be done and included in the robust summary.

Summary: No testing is proposed. The robust summary will provide technical discussions of the environmental fate characteristics (biodegradation, photodegradation, hydrolysis and fugacity) of substances in the grease thickeners category.

EVALUATION OF ECOTOXICITY AND PROPOSED TESTING

As explained in the category description above, the grease thickening agents Included in this category do not exist outside of the grease matrix, but are synthesized within the grease by adding one of several varieties of fatty acids (e.g., stearic acid, ricinoleic acid – i.e., castor oil, etc.) and metal hydroxides (e.g., lithium, calcium) to mineral oil. The caustic and fatty acid react within the mineral oil medium to form an insoluble metal salt of the fatty acid. Such “in situ” generation of the thickening agents limits the potential for environmental exposure to these substances since they are entrained within the grease matrix. In addition, fatty acids and metals used in these products are resistant to “bleed-out” (i.e., disperse from the grease matrix), as this would compromise the performance characteristics of the grease.

Summary: No testing is proposed. A technical discussion will be prepared for the robust summary that describes the potential for substances in this category to affect aquatic organisms. Aquatic toxicity data on the dissociation products of these grease thickeners, i.e., lithium, calcium, and the associated fatty acids will be included in the discussion along with relevant physicochemical information affecting their distribution in aquatic environments.

TABLE 3. MATRIX OF AVAILABLE ADEQUATE DATA AND PROPOSED TESTING FOR SELECTED TEST MATERIAL

Test	Calcium salts in this category	Li 12-hydroxy stearate in grease	Other lithium salts in this category
Melting Point	Model	Model	Model
Boiling Point	Model	Model	Model
Vapor Pressure	Model	Model	Model
Partition Coefficient	Model	Model	Model
Water Solubility	Model	Model	Model
Photodegradation	Model	Model	Model
Stability in Water	TD	TD	TD
Transport and Distribution	Model	Model	Model
Biodegradation	TD	TD	TD
Acute Toxicity to Fish	TD	TD	TD
Acute Toxicity to Aquatic Invertebrates	TD	TD	TD
Toxicity to Algae	TD	TD	TD
Acute Toxicity	Adequate	Adequate	Read-across [C]
Repeated Dose	Adequate	Adequate	Read-across [C]
Genotoxicity, *in vitro*	Adequate	Read-across [C]	Read-across [C]
Genotoxicity, *in vivo*	Adequate	Read-across [C]	Read-across [C]
Repro/ Developmental	Adequate	**TEST**	Read-across [C]

Adequate Indicates adequate existing data.
Test Indicates proposed testing
Model Indicates data will be obtained with EPA approved models
C Indicates category read-across from existing or proposed test data
TD Technical discussions will be developed to address these endpoints as appropriate.

There are no studies available on the developmental and reproductive toxicity of the lithium salts of fatty acids in the Grease Thickeners Category. Therefore, this study plan proposes reproductive/ developmental toxicity screening tests in rats (OECD 421) by the dermal route of exposure. Dermal exposure was selected as the route by which humans are most likely to come in contact with the salts of fatty acids in greases. The test material will be a grease made from USP white mineral oil thickened with approximately 12% lithium 12-hydroxystearate. No additives will be present. A lithium salt thickened grease was selected because, in the lubricant industry, the salts of fatty acids are only produced *in situ* in the mineral oil matrix, and are not synthesized separately.

REFERENCES

Barkley, W. and Stemmer, K. 1982-1984. The Carcinogenic Evaluation of Certain Petroleum Products PARL-23. Conducted by Kettering Laboratory for Texaco. Inc.

Cosmetic Ingredient Review Panel. 1982. Final Report of the Safety Assessment of Lithium Stearate, Aluminum Distearate, Aluminum Stearate, Aluminum Tristearate, Ammonium Stearate, Calcium Stearate, Magnesium Stearate, Potassium Stearate, Sodium Stearate, and Zinc Stearate. *J. Amer. College Toxicol*. 1:143-177.

Gottschewski, G.H.M. 1967. Can Carriers of Active Ingredients in Coated Tablets Have Teratogenic Effects? *Arznelm. Forsch*. 17:1100-1103.

Huntingdon Life Sciences. 1977. A Subchronic (90-Day) Toxicity Study of R960002575 in the Rat Via Oral Gavage Administration. Conducted for Texaco Lubricants Company, Study No. 96-2471.

Huntingdon Life Sciences. 1997a. A 28-Day Dermal Toxicity Study of R960002575 in the Rat. Conducted for Texaco Lubricants Company, Study No. 96-2470.

Huntingdon Life Sciences. 1997b. A 90-Day Dermal Toxicity Study of R960002575 in the Rat. Conducted for Texaco Lubricants Company, Study No. 96-2472.

Léonard, A., Hantson, P.H., and Gerber, G.B. 1995. Mutagenicity, Carcinogenicity and Teratogenicity of Lithium Compounds. *Mut. Res*. 339:131-137.

Litton Bionetics. 1976. Mutagenic Evaluation of Compound FDA 75-33, Magnesium Stearate. Report prepared under DHEW contract No. FDA 223-74-2104, Kensington, MD.

NTP. 1992. Toxicity Studies of Castor Oil (CAS No. 8001-79-4) in F344/N Rats and B6C3F1 Mice (Dosed Feed Studies). U.S. National Technical Information Service Report No. PB93-151439.

Pharmakon USA. 1994a Acute Exposure Oral Toxicity PH 402-TX-020-94. Conducted for Texaco, Inc.

Pharmakon USA. 1994b. Acute Exposure Dermal Toxicity PH 422-TX-020-94. Conducted for Texaco, Inc.

Pharmakon USA. 1994c. Primary Eye Irritation PH 421-TX-018-94. Conducted for Texaco, Inc.

Pharmakon USA. 1994d. Primary Dermal Irritation Study PH 420-TX-019-94. Conducted for Texaco, Inc.

Pharmakon USA. 1997. Delayed Contact Hypersensitivity in Guinea Pigs (Buehler) 0424XT02.005 PARL-470-92-2014. Conducted for Texaco, Inc.

Søndergaard, D., Meyer, O. and Würtzen, G. 1980. Magnesium Stearate Given Perorally to Rats. A Short Term Study. *Toxicol*. 17:51-55.